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Systematic Review
Dental Implants

Role of local alendronate delivery on the osseointegration of implants: a systematic review and meta-analysis☆

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Abstract. There is controversy regarding whether locally delivered alendronate enhances osseointegration. The aim of this systematic review was to assess the role of local alendronate delivery (topical, or as a coating on implant surfaces) in the osseointegration of implants. The focused question was, ‘‘Does the local delivery of alendronate affect osseointegration around implants?”. To address this question, indexed databases were searched, without time or language restriction, up to and including January 2017. Various combinations of the following key words were used: ‘‘alendronate”, ‘‘bisphosphonates”, ‘‘osseointegration”, and ‘‘topical administration”. letters to the editor, historic reviews, commentaries, case series, and case reports were excluded. In total, 18 experimental studies were included: alendronate-coated implants were used in 13 of these studies and local delivery in five studies. The results of 11 of the studies showed that alendronate coating increased new bone formation, the bone volume fraction, or bone-to-implant contact (BIC) and biomechanical properties. Results from two studies in which alendronate was administered topically indicated impaired BIC and/or biomechanical fixation around implants. On experimental grounds, local alendronate delivery seems to promote osseointegration. From a clinical perspective, the results in animal models support phase 1 studies in healthy humans (without co-morbidities other than edentulism).

Key words: bisphosphonates; osseointegration; implants; alendronate; topical administration.

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Dental implants are a predictable and successful treatment strategy for the replacement of missing teeth in partially and totally edentulous patients[1]. Local factors that may influence the overall success and survival of implants include primary stability at the time of implant placement, the formation of a direct bone to implant contact (BIC)[2], and the quantity and/or quality of the residual bone[3]. Substantial efforts have been made to accelerate healing around implants. In this regard, adjunct therapies such as the placement of osteogenic coatings on implant surfaces[3–6]

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have been proposed in an attempt to enhance BIC and new bone formation (NBF) around implant surfaces. Modifications in implant surface chemistry have also been reported to enhance the proliferation and differentiation of osteoprogenitor cells and to increase alkaline phosphatase (ALP) activity and the expression of osteogenic genes (which helps to enhance BIC and promote osseointegration)[7]. Such implant surface modifications have been shown to improve osseointegration in systemically healthy as well as immunosuppressed patients, such as those with osteoporosis or poorly controlled diabetes mellitus[8–10].

Alendronate, which belongs to the bisphosphonate class of drugs, is an anticatabolic agent that inhibits bone resorption and is therefore widely used for the treatment of skeletal disorders such as osteoporosis, bone metastases, and Paget's disease[11]. It has been suggested that alendronate influences the three phases of bone remodeling, which are microinjury, osteoclastogenesis, and osteogenesis, thereby stimulating NBF by enhancing the proliferation and differentiation of osteoblasts and inhibiting osteoclast function[12,13]. In addition to the bone antiresorptive effect, in vitro studies have shown that the administration of alendronate modulates osteoprotegerin (OPG) production by fibroblasts[14], and decreases phosphatase activity and the expression of osteoclast markers[15].

According to Hazzaa et al., the systemic administration of alendronate significantly improves osseointegration around titanium implants placed in animals with induced osteoporosis[16]. A recent systematic review also concluded that systemic bisphosphonate supplementation promotes implant osseointegration in animals with induced osteoporotic conditions[17]. However, in a clinical scenario, the potential risk of bisphosphonates related to osteonecrosis of the jaw cannot be disregarded[17]. Other complications related to the systemic administration of alendronate such as nausea, epigastric pain, vomiting, and dyspepsia, could be avoided by local alendronate release directly from the implant to the surrounding bone[18].

Conflicting results have been reported regarding whether local alendronate delivery (topical, or as a coating on implant surfaces) enhances osseointegration and NBF around implants[18–35]. Therefore, the aim of this systematic review was to assess the role of local alendronate delivery (topical, or as a coating on implant surfaces) in the osseointegration of implants.

Materials and methods

Focused question

Based on the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[36], a specific question was constructed according to the PICO principle (participants, interventions, control, outcomes). The focused question was, ''Does the local delivery of alendronate affect osseointegration around implants?" Participants (P) had to have undergone implant treatment. The intervention of interest (I) was the effect of local delivery of alendronate on osseointegration. The control intervention (C) was implant placement without adjunctive local alendronate administration. Outcome measures (O) included BIC, NBF, bone volume/tissue volume (BV/TV), and/or biomechanical fixation around implants with and without alendronate local delivery.

Eligibility criteria

The eligibility criteria were as follows: (1) original studies, (2) randomized controlled trials, (3) prospective and retrospective studies, (4) cohort studies, (5) experimental studies (animal models), (6) studies with a control group, (7) intervention: effect of local alendronate (topical or coating) on osseointegration. Letters to the editor, historic reviews, commentaries, in vitro studies, case series, case reports, and studies where alendronate was delivered systemically were excluded. Articles available online in electronic form ahead of print were considered eligible for inclusion.

Literature search protocol

In order to identify studies relevant to the focused question, an electronic search without time or language restriction was conducted in January 2017 in the PubMed (National Library of Medicine, Washington, DC, USA), Google Scholar, Scopus, Embase, MEDLINE (OVID), and Web of Knowledge databases. The following medical subject headings (MeSH) were used: (1) alendronate, (2) bisphosphonates, (3) osseointegration, (4) topical administration, and the combinations 1 or 2 and 3; 1 or 2 and 4; and 1, 2, and 3 or 4. Other relevant non-MeSH words were used in the search process to identify articles discussing osseointegration parameters and/or alendronate administration. These included: ''local delivery", ''local administration", ''coating", ''coated", ''bone-to-implant contact", and ''new bone formation".

Titles and abstracts of studies identified using the protocol described above were screened by two authors (SVK and VRM) and checked for agreement to exclude irrelevant articles and duplicates. The full texts of studies judged by title and abstract to be relevant were read and evaluated independently for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify studies that had remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors. Kappa scores (Cohen's kappa coefficient) were used to determine the level of agreement between the two reviewers ($\kappa = 0.90$)[37]. Data were extracted using standardized evaluation forms. Authors of the studies included were contacted via e-mail in the case of missing data or for additional information regarding their studies if required. Fig. 1 summarizes the literature search strategy according to the PRISMA guidelines.

Quality assessment

A quality assessment of the studies that were included was performed in an attempt to increase the strength of the systematic review. The studies that were included underwent a quality assessment with the Critical Appraisal Skills Program (CASP) cohort study checklist[38]. The CASP tool uses a systematic approach based on 12 specific criteria, which are (1) study issue is clearly focused (effect of local alendronate delivery on osseointegration); (2) cohort is recruited in an acceptable way; (3) exposure (alendronate delivery) is accurately measured; (4) outcome (osseointegration and/or NBF around implants) is accurately measured; (5) confounding factors are addressed; (6) follow-up is long and complete; (7) results are clear; (8) results are precise; (9) results are credible; (10) results can be applied to the local population; (11) results fit with available evidence; and (12) there are important clinical implications. Each criterion was given a response of either 'yes', 'no', or 'cannot tell'. Each study could have a maximum score of 12. CASP scores were used to grade the methodological quality of each study assessed in the present systematic review.

Data analysis

A meta-analysis was performed for four studies in which the effect of local alen-

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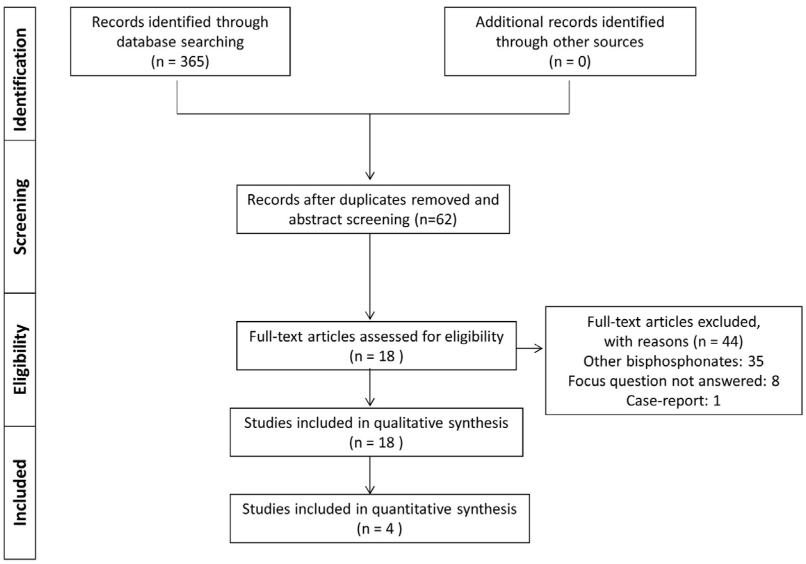

Fig. 1. Flowchart of the article selection for this systematic review, according to the PRISMA guidelines.

dronate on BIC was assessed[22,31–33]. The heterogeneity in the treatment difference between control and treatment groups across the studies was assessed using the Q statistic. The random-effects meta-analysis model was used to combine the results from the different studies[39]. The data analysis was conducted using OpenMetaAnalyst version 6 software (Center for Evidence Synthesis, Brown School of Public Health, Providence, RI, USA).

Results

Study selection

Three hundred and sixty-five potential articles were initially identified. In the first step, 303 publications, which were either duplicates or did not answer the focused question, were excluded. In the next step, 44 further articles were excluded (**Supplementary Material**). In total, 18 studies were included and processed for data extraction[18–35].

General characteristics of the studies included

All studies were prospective and performed in animals. Three studies were performed in male rats[23,27,29], three in male rabbits[22,32,33], and one in female rabbits[21]; the sex of the rabbits was unclear in one study[35]. Two studies were performed in sheep and the sex was not reported[20,28]. Four studies were performed in female dogs[24–26,34], two in male dogs[30,31], and two in female and male dogs[18,19]. In all studies, alendronate was delivered locally. Alendronate-coated implants were used in 13 studies[18–21,23,27–33,35], and intra-cavity injections of alendronate were administered in four studies[22,25,26,34]. A morselized allograft soaked in alendronate solution was used in one study[24]. The follow-up period in all studies ranged between 2 and 24 weeks.

Topical delivery of alendronate

An alendronate solution (2 mg alendronate per 1 ml saline) was injected into the bone cavity 60 s prior to implant placement in three studies[25,26,34]. Sodium alendronate gel (10 mg/g) was injected into the surgical alveolus before implant placement in one study[22]. Jakobsen et al. investigated the effects of morselized allograft soaked with 5 ml alendronate solution packed in a 2.5-mm gap around titanium implants placed in the humerus in a canine model[24].

Implants with alendronate-coated surfaces

In 13 studies, alendronate was incorporated as a coating on the implant surfaces, with a concentration ranging between 0.02 mg and 1 mg (Table 1)[18–21,23,27–33,35]. The alendronate was incorporated into hydroxyapatite-coated implants in five studies[18,30–33] and into calcium phosphate (CaP)-coated implants in two studies[21,29].

Implant-related characteristics of the studies included

Titanium implants were used in 16 studies[18–20,22–28,30–35], with two of these studies using mesoporous titanium to serve as the drug carrier[23,27]. Garbuz et al. placed porous tantalum in the rabbit femur[21]. Linderback et al. placed stainless steel screws in rat tibiae[29]. Zirconium implants were used as controls in two studies[20,28]. Twelve studies reported the total numbers of implants placed in the subjects, which ranged from 16 to 110 implants[19–22,24–26,28,30,31,34,35]. The total number of implants placed was not reported for six studies[18,23,27,29,32,33]. Implants were placed in the tibia in nine studies[22,23,25–27,29,32,33,35] and in the femur in four[18,19,21,34]. In the studies by Ferguson et al.[20] and Langhoff et al.[28], implants were placed in sheep pelvis. Meraw et al.[30,31] placed the implants in the dog mandible and Jakobsen et al.[24] placed implants in the dog humerus.

The implant dimensions were reported for 14 studies, with the diameter × length of the implants used ranging between 1.7 × 2.5 mm and 9 × 90 mm[18–26,29,32–35]. Four studies did not report the dimensions of implants used[27,28,30,31]. Cylindrical implants were placed in 11 studies[18–21,24–26,32–35] and screw-type implants in three studies[22,23,29]. The shape of the implants used was not reported in four studies[27,28,30,31]. Rough-surface implants were used in 16 studies[18–29,32–35], and implants with smooth and rough surfaces were used in the two studies by Meraw et al.[30,31] (Table 2).

Assessment of osseointegration

Eleven studies assessed osseointegration using histomorphometric analysis[21–26,30–34]. Biomechanical testing was performed to assess the strength of newly formed bone around implants in 10 studies[20,22–26,29,32–34]: three studies used removal torque analysis[20,22,23], six used the push-out test[24–26,32–34], and one study used a pull-out test[29] to assess osseointegration. NBF around implants was assessed using three-dimensional micro-computed tomography (micro-CT) in four studies[19,20,32,35]. In nine studies, osseointegration was assessed using histology[18,19,22,23,28,30–32,35]. NBF around implants was assessed using backscattered electron microscopy in three studies[18,19,27] and fluorescence microscopy in one study[21]. In three studies, fluorescence markers were used to track patterns of NBF and apposition[21,28,31]. Harmankaya et al. used quantitative polymerase chain reaction and ultrastructural interface analysis to assess the osteogenic response after 4 weeks of implantation[23]. Karlsson et al. used micro-Raman spectroscopy to assess NBF[27]. In

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Table 1. Studies on the local delivery of alendronate.

Authors (Study design)	Study subjects (Mean age)	Study groups	Bisphosphonate doses and concentrations	Follow-up, weeks	Analysis methods	Outcomes
Implants with an alendronate-coated surface						
Bobyn et al.[19]	10 male and female dogs (NA)	Group 1: uncoated Ti	ALE: 0.2 mg	12	Micro-CT	Groups 2 and 3 presented significantly higher NBF compared to group 1
(Experimental)		Group 2: ALE 0.2 mg Group 3: ALE 1 mg	ALE: 1 mg		Histology BEM	
Ferguson et al.[20]	Sheep (NA)	Group 1: uncoated Ti	Group 5: ALE 10 µg/cm^2	2, 4, and 8	Removal torque	Groups 1, 3, 5, and 6 presented significantly higher removal torque compared to groups 2 and 4
(Experimental)		Group 2: uncoated Zr			Micro-CT	Outcomes in BV/TV were comparable among the groups
		Group 3: Ti + CaP Group 4: Ti + CaP + APC Group 5: Ti + ALE Group 6: Ti + collagen + CS				
Garbuz et al.[21]	18 female rabbits	Group 1: uncoated Ta	Group 3: ALE 10^{-4} M	4	Fluorescence	Group 3 presented higher NBF, gap filling, and bone ingrowth compared to groups 1 and 2
(Experimental)	(NA)	Group 2: Ta + CaP Group 3: Ta + CaP + ALE			HIST BEM–FM	
Harmankaya et al.[23]	32 male rats (NA)	Group 1: mesoporous TiO_2	Group 2: ALE 0.8 mg/ml	4	Removal torque	Group 2 presented significantly higher BA compared to groups 1, 2 and 3
(Experimental)		Group 2: mesoporous TiO_2 + ALE			Histology	No significant difference in BIC among the groups
		Group 3: mesoporous TiO_2 + RLX			HIST	Group 2 presented increased removal torque compared to groups 1 and 4
		Group 4: hydrophobic mesoporous TiO_2			qPCR	
					UIA	
Karlsson et al.[27]	Male rats	Group 1: mesoporous TiO_2 + ALE	Group 1: ALE 0.8 mg/ml, 170 ng per implant	4	Micro-Raman spectroscopy	Group 1 presented higher BMD and NBF compared to group 2
(Experimental)	(NA)	Group 2: mesoporous TiO_2			BEM–SEM	
Kim et al.[35]	12 rabbits	Group 1: uncoated Ti	Groups 2 and 4: ALE 10^{-6} M	8	Micro-CT	Group 4 presented higher BA and NBF compared with groups 1, 2, and 3
(Experimental)	(3 months old)	Group 2: Ti + ALE Group 3: Ti + UV Group 4: Ti + UV + ALE			Histology	
Langhoff et al.[28]	15 sheep	Group 1: uncoated Ti	Group 5: ALE 10 µg/cm^2	2, 4, and 8	Fluorescence	No significant difference in BIC among the groups
(Experimental)	(24–36 months old)	Group 2: Ti + CaP coated			Radiographs	
		Group 3: Ti + CaP + APC Group 4: Ti + collagen + CS Group 5: Ti + ALE Group 6: uncoated Zr			Histology	

Linderback et al.[29]	40 male rats	Group 1: uncoated SS	Group 4: ALE 0.1 mg/ml	4	Pull-out test	Group 4 presented significantly higher strength of fixation compared to groups 1, 2, and 3
(Experimental)	(NA)	Group 2: SS + TiO_2 + CaP Group 3: SS + TiO_2 + CaP + systemic ALE Group 4: SS + TiO_2 + CaP + local ALE				
Meraw et al.[31] (Experimental)	6 male dogs (NA)	Group 1: HA + ALE	Group 1: ALE 0.1 mmol	4	Fluorescence	Group 3 presented higher BIC compared to groups 1, 2, and 4
		Group 2: uncoated Ti + ALE	Group 2: ALE 2.8 μg		HIST	Group 2 presented higher BIC compared to group 4
		Group 3: HA			Histology	Groups 1 and 2 presented significantly higher NBF compared to groups 3 and 4
		Group 4: uncoated Ti				
Meraw et al.[30]	6 male dogs	Group 1: HA + ALE	Group 1: ALE 0.1 mmol	4	Histology	Group 2 presented significantly higher BA compared to groups 1, 3, and 4
(Experimental)	(NA)	Group 2: uncoated Ti + ALE	Group 2: ALE 2.8 μg		HIST	
		Group 3: HA Group 4: uncoated Ti				
Niu et al.[33]	36 male rabbits	Group 1: HA + IPP	Group 2: ALE 100 μg	12 and 24	HIST	Group 2 presented significantly higher BIC, NBF, BMD, and implant stability compared to groups 1 and 3 after 24 weeks
(Experimental)	(NA)	Group 2: HA + IPP + ALE	Group 3: RIS 50 μg		Push-out test	Groups 2 and 3 presented significantly higher BV/TV compared to group 1
		Group 3: HA + IPP + RIS			ELISA	
Niu et al.[32]	30 male rabbits	Group 1: HA	Group 3: 100 μg ALE	12	HIST	Group 3 presented higher BV/TV, MAR, BIC, NBF, and implant stability compared to groups 1 and 2
(Experimental)	(NA)	Group 2: HA + IPP Group 3: HA + IPP + ALE			Histology Micro-CT Push-out test	
Pura et al.[18]	8 male dogs and six female dogs	Group 1: uncoated Ti	ALE	12	Histology	Groups 4 and 5 presented higher bone ingrowth compared to groups 1, 2 and 3
(Experimental)	(3–9 years old)	Group 2: HA	Group 3: 0.02 mg/cm^2		BEM–SEM	Group 4 presented higher bone apposition compared to groups 1, 2, 3, and 5
		Group 3: HA + ALE 0.02	Group 4: 0.06 mg/cm^2			
		Group 4: HA + ALE 0.06	Group 5: 0.18 mg/cm^2			
		Group 5: HA + ALE 0.18				
Topical delivery of bisphosphonates						
Guimaraes et al.[22]	10 male rabbits	Group 1: uncoated Ti	Group 2: 1 ml ALE gel (10 mg/g), intra-cavity injection	4	Removal torque	Group 2 presented significantly lower removal torque values, BIC, and NBF compared to group 1

Table 1 (*Continued*)

Authors (Study design)	Study subjects (Mean age)	Study groups	Bisphosphonate doses and concentrations	Follow-up, weeks	Analysis methods	Outcomes
(Experimental)	(NA)	Group 2: uncoated Ti + ALE gel			Histology HIST	
Jakobsen et al.[24]	10 female dogs	Group 1: cancellous allograft soaked with saline	Group 2: 5 ml ALE solution (2 mg ALE × 1 ml saline); soaked morselized allograft	4 and 12	HIST	Group 2 presented significantly decreased biomechanical fixation, BIC, and NBF compared to group 1
(Experimental)	(NA)	Group 2: cancellous allograft soaked with ALE			Push-out test	
Jakobsen et al.[26]	10 female dogs	Group 1: saline	Group 2: 5 ml ALE solution (2 mg ALE × 1 ml saline); intra-cavity injection (60 s)	12	Bacterial culture	Group 2 presented significantly higher biomechanical fixation, BIC, and BVF compared to group 1.
(Experimental)	(NA)	Group 2: ALE			HIST Push-out test	
Jakobsen et al.[25]	10 Female dogs	Group 1: saline	Group 2:	12	Push-out test	Group 2 presented significantly higher biomechanical fixation, and BVF compared to group 1
(Experimental)	(NA)	Group 2: ALE	5 ml ALE solution (2 mg ALE x 1 ml saline) Intra cavity injection (60 seconds)		HIST	No significant difference in BIC between groups 1 and 2
Jakobsen et al.[34]	8 female dogs	Group 1: saline	Group 2: 15 ml ALE solution (1 mg ALE × 1 ml saline); intra-cavity injection (60 s)	4	Push-out test	Group 2 presented significantly higher BIC and BA compared to group 1
(Experimental)	(11.5 months old)	Group 2: ALE			HIST	No significant difference in strength of fixation between groups 1 and 2

ALE, alendronate; APC, anodic plasma–chemical surface modification; BA, bone area; BEM, backscattered electron microscopy; BIC, bone-to-implant contact; BMD, bone mineral density; BVF, bone volume fraction; BV/TV, bone volume/tissue volume; CaP, calcium phosphate; CS, chondroitin sulfate; ELISA, enzyme-linked immunosorbent assay; FM, fluorescence microscopy; HA, hydroxyapatite; HIST, histomorphometry; IPP, injected polyethylene particles; MAR, mineral apposition rate; Micro-CT, micro-computed tomography; NA, not available; NBF, new bone formation; qPCR, quantitative polymerase chain reaction; RIS, risedronate; RLX, raloxifene; SEM, scanning electron microscope; SS, stainless steel; Ta, tantalum; Ti, titanium; TiO_2, titanium dioxide; UIA, ultrastructural interface analysis; UV, ultraviolet treatment; Zr, zirconia.

Table 2. Characteristics of the implants used in the studies.

Authors	Number and material of implants	Implant dimensions (diameter × length, mm)	Location of implant placement	Implant shape	Implant surface characteristics
Bobyn et al.[19]	20 Ti	9 × 90	Femur	Cylinder	Rough
Ferguson et al.[20]	90 Ti 18 Zr	4.2 × 8	Pelvis	Cylinder	Rough
Garbuz et al.[21]	36 Ta	3.18 × 8	Femur	Cylinder Gap model	Rough
Guimaraes et al.[22]	50 Ti	2.2 × 4	Tibia	Screw	Rough
Harmankaya et al.[23]	Ti (NA)	2 × 2.3	Tibia	Screw	Rough (mesoporous TiO_2)
Jakobsen et al.[34]	16 Ti	5.6 × 10	Femur	Cylinder	Rough
Jakobsen et al.[24]	40 Ti	6 × 10	Humerus	Cylinder Gap model	Rough
Jakobsen et al.[26]	20 Ti	8 × 10	Tibia	Cylinder	Rough
Jakobsen et al.[25]	20 Ti	8 × 10	Tibia	Cylinder	Rough (HA)
Karlsson et al.[27]	Ti (NA)	NA	Tibia	NA	Rough (mesoporous TiO_2)
Kim et al.[35]	48 Ti	4 × 6	Tibia	Cylinder	Rough
Langhoff et al.[28]	86 Ti 24 Zr	NA	Pelvis	NA	Rough
Linderback et al.[29]	SS (NA)	1.7 × 2.5	Tibia	Screw	Rough
Meraw et al.[31]	48 Ti	NA	Mandible	NA	Smooth Rough (HA)
Meraw et al.[30]	48 Ti	NA	Mandible	NA	Smooth Rough (HA)
Niu et al.[33]	Ti (NA)	2.5 × 45	Tibia	Cylinder	Rough (HA)
Niu et al.[32]	Ti (NA)	2.5 × 45	Tibia	Cylinder	Rough (HA)
Pura et al.[18]	Ti (NA)	9 × 45 and 9 × 90	Femur	Cylinder	Rough (HA)

HA, hydroxyapatite; NA, not available; SS, stainless steel; Ta, tantalum; Ti, titanium; TiO_2, titanium dioxide; Zr, zirconia.

one study, an enzyme-linked immunosorbent assay was used to measure serum levels of bone turnover markers, such as ALP, OPG, and receptor activator of nuclear factor kappa-B ligand (RANKL)[33].

Main outcomes

Topical delivery of alendronate

The results of two studies in which alendronate was administered topically (gel or soaked allograft) into the bone cavities showed that alendronate impairs NBF, BIC, and/or biomechanical fixation around implants compared to the control group[22,24]. However, the results of three studies in which alendronate solution was injected intra-cavity before implant placement, showed enhanced biomechanical fixation, BIC, and/or BV/TV around implants[25,26,34].

Implants with alendronate-coated surfaces

Results from 11 studies showed that alendronate improved NBF, BV/TV, or BIC and biomechanical properties[18,19,21,23,27,29–33,35]. However, three studies reported no significant difference in BIC between uncoated titanium implants and alendronate-coated titanium implants[23,28,31]. Ferguson et al. reported comparable BV/TV values among titanium implants coated with alendronate and those with titanium surfaces modified with CaP or collagen, and uncoated zirconium and titanium implants[20].

Quality assessment of included studies

All studies were conducted on experimental animals and the total quality assessment scores ranged from 8 to 9. The most common limitations among all studies were the short-term and incomplete follow-up (up to 24 weeks) of the experimental groups and the non-assessment of confounder variables (such as systemic conditions, habits, and age). Furthermore, as all studies were performed in animals, the application of the results to the human population was limited. On average, the quality of the animal studies included in this review on the impact of topical alendronate administration on the osseointegration of implants was good; however, the short-term follow-up, lack of confounder assessment, and need for clinical studies limit the clinical application of these study outcomes. The quality assessment of the individual papers is summarized in Table 3.

Meta-analysis

A meta-analysis was performed including the four studies that reported the mean BIC values and respective standard deviations[22,31–33]. The sample sizes were comparable in these studies[22,31–33]. Three studies reported that the mean BIC around implants with alendronate therapy (test group) was significantly higher than that in the control group (without alendronate therapy)[22,31–33]. In the remaining study, the BIC was significantly higher in the control group than in the test group[22]. The Q statistic showed that the treatment effects differed significantly among the four studies ($Q = 92.20$, $P < 0.001$). The random-effects model showed that the combined BIC in the test group was higher than that in the control group (mean difference = −13.46, $P = 0.217$) (Fig. 2).

Discussion

In this literature review, 14 out of the 18 studies, showed that local delivery of alendronate either as a socket surface coating or applied on implant surfaces enhances osseointegration[18,19,21,23,25–27,29–35]. These results suggest that local alendronate delivery improves osseointegration. However, it is noteworthy that the results of two studies in which alendronate was applied topically reported impaired BIC, NBF, and strength of fixation around the implants (Guimaraes et al.[22] and Jakobsen et al.[24]). A variety of factors may have influenced these results. The

Table 3. CASP quality assessment of the reviewed papers.

Authors	Item[a]												Total quality score
	1	2	3	4	5	6	7	8	9	10	11	12	
Bobyn et al.[19]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Ferguson et al.[20]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Garbuz et al.[21]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Guimaraes et al.[22]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	8
Harmankaya et al.[23]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Jakobsen et al.[34]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Jakobsen et al.[24]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	8
Jakobsen et al.[26]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Jakobsen et al.[25]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Karlsson et al.[27]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Kim et al.[35]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Langhoff et al.[28]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	8
Linderback et al.[29]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Meraw et al.[31]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Meraw et al.[30]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Niu et al.[33]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Niu et al.[32]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Pura et al.[18]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9

CASP, Critical Appraisal Skills Program checklist.

[a] (1) Study issue is clearly focused; (2) cohort is recruited in an acceptable way; (3) exposure is accurately measured; (4) outcome is accurately measured; (5) confounding factors are addressed; (6) follow-up is long and complete; (7) results are clear; (8) results are precise; (9) results are credible; (10) results can be applied to the local population; (11) results fit with available evidence; (12) there are important clinical implications.

methodologies and dose used to administer alendronate varied markedly among the studies[22,24–26,34]. For example, in the study by Guimaraes et al.[22] a topical application of 1 ml of alendronate gel was injected into the bone cavity prior to implant placement, whereas Jakobsen et al.[24] soaked morselized allograft in 5 ml alendronate (10 mg) solution for 3 min and packed this into the peri-implant gap. Garbuz et al. reported increased NBF, gap filling, and bone ingrowth in rabbits receiving tantalum (Ta) implants coated with CaP and alendronate, compared with uncoated Ta implants and Ta implants coated with CaP only[21]. It is possible that in the study by Guimaraes et al., the intimate contact of the alendronate gel with the bone marrow enhanced the drug toxicity in the surrounding bone, impairing NBF and osteoblastic activity[22]. Similarly, it is possible that in the study by Jakobsen et al., the increased density of allograft grains did not provide space for neovas-

Bone to implant contact							
Study	Control (without alendronate delivery)			Test (with alendronate delivery)			Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Guimaraes et al.[22]	24.55	8.59	10	9.77	6.53	10	14.780 (8.092, 21.468)
Meraw et al.[31]	30	14.9	6	59.4	7.2	6	-29.400 (-42.641, -16.159)
Niu et al.[33]	41.46	9.15	12	51.82	7.09	12	-10.360 (-16.909, -3.811)
Niu et al.[32]	20	8	10	50	8	10	-30.000 (-37.012, -22.988)
Total			38			38	-13.464 (-34.839, 7.911)

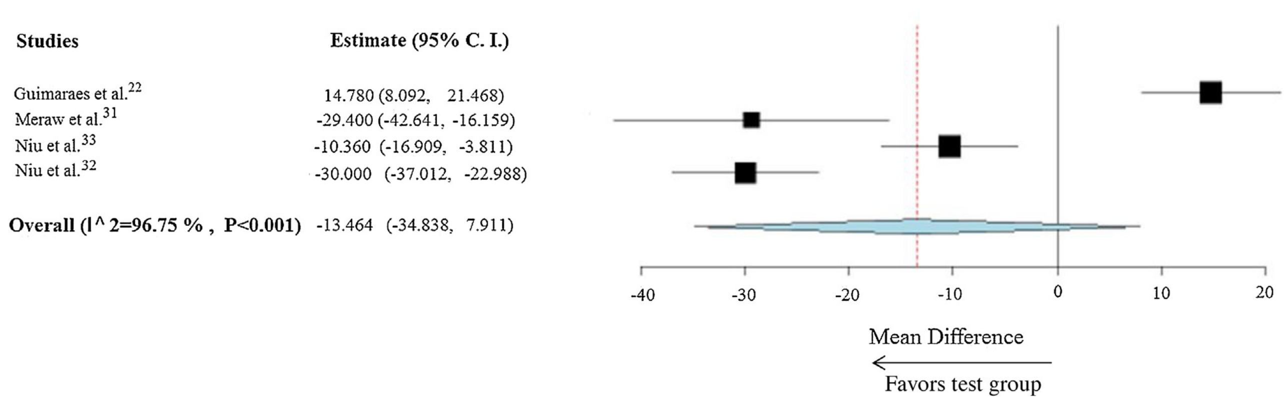

Fig. 2. Forest plot presenting the mean difference (MD) of bone-to-implant contact between the test and control groups.

culogenesis and that the alendronate dose in which the allograft was soaked was too high[24]. Moreover, Jakobsen et al. did not rinse the soaked allograft with saline and did not measure the amount of alendronate absorbed by the allograft[24]. This shows the lack of standardization regarding the methods to deliver alendronate topically among the studies included, which should be taken into consideration in future protocols investigating the clinical use of alendronate in implantology.

All of the studies that assessed the effect of local alendronate delivery on osteogenesis around implants were performed in animal models. Moreover, the methodologies used to assess osseointegration varied among the studies. For example, some studies assessed NBF using histological analysis[18,19,22,23,28,30–32,35], and others used micro-Raman spectroscopy[27] or fluorescence analysis[21,28,31] to assess osseointegration. Although a variety of methods can be used to assess BIC and NBF (such as biomechanical testing, resonance frequency analysis, micro-CT), histological evaluation continues to be the gold standard for the assessment of osseointegration at the cellular level[40]. This shows that a definitive methodology to assess bone formation around implants (with or without alendronate supplementation) is yet to be formulated.

The follow-up period in all studies included in this systematic review was relatively short (up to 24 weeks). It is hypothesized that had these experimental studies been followed-up for longer durations, they would have provided stronger evidence regarding the efficacy of local alendronate delivery on the osseointegration of implants.

Bisphosphonates as a drug class share several common properties; however, there are obvious chemical, biochemical, and pharmacological differences among the individual bisphosphonates, in terms of speed and duration of action[41,42]. Nancollas et al. proposed a bisphosphonate ranking order according to their mineral-binding capacity: zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate[43]. Moreover, Wermelin et al. reported enhanced NBF and biomechanical properties around implants coated with fibrinogen and a combination of pamidronate and ibandronate compared with uncoated controls[44]. It is noteworthy that among all the studies included, only Niu et al. compared the efficacy of alendronate versus other bisphosphonate coatings (risedronate) in promoting NBF[33]. Therefore, studies comparing the local delivery efficacy of different bisphosphonates to improve osseointegration are needed.

Since all studies included in this systematic review were performed in animals, it remains debatable whether or not the local delivery of alendronate in a clinical scenario would improve osseointegration in humans. Moreover, bisphosphonates and other antiresorptive drugs are considered a major risk factor for the development of medication-related osteonecrosis of the jaw (MRONJ) among patients undergoing dentoalveolar surgery, such as tooth extractions and dental implant placement[45,46]. Regardless of the fact that low doses of alendronate are needed to enhance osseointegration, the potential risk of MRONJ associated with local alendronate therapy cannot be disregarded. More standardized studies are needed to provide more accurate information.

In conclusion, on experimental grounds, local alendronate delivery seems to promote osseointegration. From a clinical perspective, the results in animal models support phase 1 studies in healthy humans (without co-morbidities other than edentulism).

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Competing interests

The authors declare no competing interests.

Ethical approval

No ethical approval was needed for this study.

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijom.2017.03.009.

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